## REMARKS

Claims 1-80 are pending in this application, and of those claims 18-79 were withdrawn from consideration as being drawn to a non-elected invention. In view of the examiner's earlier restriction requirement, applicant retains the right to present claims 18-79 in a divisional application. Correction of the title is requested so that the new title is clearly indicative of the invention to which the claims are directed. Correction of the Drawings for Figures 2, 13, and 16 is required for unacceptable margins. Claims 2 and 11 are rejected under 35 U.S.C. § 112, second paragraph. Claims 1-8, 10-17 and 80 are rejected under 35 U.S.C. § 102 (b) as anticipated by Korth *et al.* (Nature, 1997, IDS Paper No. 7). And, claims 1-17 and 80 are rejected under 35 U.S.C. § 102 (a) as anticipated by Korth *et al.* (WO 98/37210, see IDS) or under 35 U.S.C. § 102 (b) by Korth *et al.* (EP 0 861 900, see IDS). These requests, objections, and rejections are addressed below.

Request for Title Correction.

Correction of the title was requested so that the new title is clearly indicative of the invention to which the claims are directed. The applicants respectfully submit "An Epitope Selective for Pathogenic Prion Protein" as an appropriate new title for the application in response to the request for correction.

Objection to Drawings

Correction of the Drawings for Figures 2, 13, and 16 is required for unacceptable margins. The depictions in Figures 2 and 13 have been slightly reduced in size so as to permit acceptable margin widths without appreciable change in the discernability of their content. In the case of Figure 16, panels A and B were realigned vertically rather than horizontally. The replacement drawings are respectfully submitted for consideration, and are accompanied by annotated copies of the originals illustrating the changes made.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2 and 11 were rejected as indefinite because the specification does not provide a standard of measuring the degree intended by the phrase "does not substantially bind $PrP^{C}$", thereby rendering the scope of the claims unascertainable. This rejection has been met by the present amendment, which adds new claims "wherein said antibody selectively binds $PrP^{Sc}$ as compared to $PrP^{C}$", and amends the current claims to read "does not specifically bind $PrP^{C}$" rather than "does not substantially bind $PrP^{C}$". An explanation of these changes follows.

Limitations are not directly defined in the specification for "substantial binding" to $PrP^{C}$. The applicants believe that the degree to which binding to $PrP^{Sc}$ relative to $PrP^{C}$ is relevant to different uses of the antibodies is likely to vary greatly with the uses and advancing technologies and would thus be difficult to predict, thus "substantial binding" was intended as a reasonably clear and precise (MPEP 2173.05(e)) standard encompassing the two types of relative binding

focused on in the application, which might be described as isoform-favored and isoform-specific binding. However, the applicants note that the choice of the term might have rendered the connection between "substantial binding" and the standards provided for measuring (MPEP 2173.05(b)) the isoform-favored binding ("selective" binding) and isoform-specific binding (specific binding of $PrP^{Sc}$, but not specific binding of $PrP^{C}$) less than clear. It should also be noted that "selective" is used as a term of art here synonymous with some of the uses of "specific" within the specification. Determining specificity is in part a determination that an antibody is in some way selective, as in "Testing of pAbC2 in an ELISA" (p. 30), where specific recognition of $PrP^{Sc}$ is compared to specific recognition of $PrP^{C}$ and the results can also indicate selectivity for $PrP^{Sc}$ relative to $PrP^{C}$.

The first of the two types of binding focused on in the application is binding that is selective for $PrP^{Sc}$ over $PrP^{C}$ -- that discriminates between $PrP^{Sc}$ and $PrP^{C}$ in a manner that favors binding to $PrP^{Sc}$ (e.g. (p. 3) "The availability of antibodies that distinguish $PrP^{C}$ from $PrP^{Sc}$ would therefore be of great value in development of a test for prion infection."). Outside this group, for example, is "non-distinguishing PrP monoclonal antibody 6H4" (p. 10) (note also, "6H4 (lanes 13-15) is an anti-PrP monoclonal antibody that does not discriminate $PrP^{C}$ from $PrP^{Sc}$" (p. 11)). Selective binding is determined by methods described in the specification and in incorporated references, such as Korth *et al.* Nature (1997) *390*: 74-77 (p. 16). For example, one skilled in the art can distinguish the relative binding of an antibody to $PrP^{Sc}$ and $PrP^{C}$ by immunoprecipitation coupled with immunoblotting as in Figure 9, where the binding of the antibody to the $PrP^{Sc}$ and $PrP^{C}$ forms of the PrP protein can be compared, and preferential binding for $PrP^{Sc}$ relative to $PrP^{C}$ assessed. This example should not be considered limiting.

The other type of binding is a subset of selective binding: antibodies that are not only selective for $PrP^{Sc}$ as compared to $PrP^{C}$, but that also do not specifically bind $PrP^{C}$ (e.g. (p. 4) "In addition, the invention relates to antibodies that selectively bind to disease-specific prion protein and not normal prion protein."). The applicants respectfully submit that a limitation to not specifically binding $PrP^{C}$ defines this limit experimentally in that binding to $PrP^{C}$ may occur, so long as binding to $PrP^{C}$ is reproducibly not considered significantly different and readily distinguishable from non-specific binding as determined by methods present in the specification or incorporated by reference. For example, immunoprecipitation coupled with immunoblotting can be used to determine $PrP^{C}$ binding relative to non-specific binding, usually represented by an appropriate control condition, or simply through a lack of significant or detectable binding to $PrP^{C}$ as in Figures 9 and 16 or in Figure 7. Examples, not to be taken as limiting, of an assay with a control would include Figures 6 and 9 of the specification, Figure 1 of Korth *et al.* Nature (1997) *390*: 74-77, and experiments using saturating antigen peptide competition to the antibody in question. To make clear the standards of measuring for these two types of binding which are present in the specification and that were intended to be covered with "substantial binding", the applicants respectfully submit amended versions of claims 2 and 11, and note amended versions of the corresponding withdrawn claims 19 and 48, which also utilize the term "substantial binding", should also be amended when they are elected. Additional claims 81 and 82 are also included, so that the intended scope of the original claims are not unduly compromised, but new matter is also not incorporated. Similarly, additional claims should accompany claims 19 and 48 when they are elected.

For all of the aforementioned reasons, applicants request reconsideration on this issue and withdrawal of the 35 U.S.C. § 112, second paragraph rejection.

Rejections Under 35 U.S.C. § 102 (a) and (b)

Claims 1-8, 10-17 and 80 were rejected under 35 U.S.C. § 102 (b) as anticipated by Korth *et al.* (Nature, 1997, IDS Paper No. 7). In particular, the Examiner asserts that the 15B3 and 6H4 antibodies are both relevant to the application, and are antibodies of high binding affinity against a YYR epitope. These assertions contradict what is known about these antibodies specifically, and some reasonable assumptions based on knowledge of the art. In view of the clear distinctions between applicants' high affinity anti-YYR antibodies and Korth *et al.*'s 15B3 and 6H4 antibodies, this rejection is respectfully traversed.

The Examiner notes, based on Figure 3 of Korth *et al.* Nature, that the15B3 and 6H4 antibodies are against a YYR epitope. 6H4 clearly does not meet the claim limitations set by our application, given the direct evidence that the 6H4 antibody does not bind to the YYR epitope present in the competition experiment of Paramithiotis *et al.* Nature Medicine (2003) *9*: 893-899, Figure 3 (present in Supplementary IDS).

For 15B3, note, in fact, that "YYR", or even "YYX" is not present in a majority of the sequences Korth *et al.* claim to contain the 15B3 epitope: "GSDYEDR", "YYRPVDQYS", "CITQYQRESQAYY", and "RPVDQYSNQNNFV" (in the European application (EP0861900)). This strongly indicates "YYR", or even "YY" by itself is not the 15B3 epitope,

nor is it part of a 15B3 epitope based on simple linear amino acid sequence. Thus, 15B3 as prior art also falls outside the claim limitations of our application.

In fact, data from Figure 2, as well as the prior differing data present in EP0861900, might be taken to indicate that a linear 15B3 epitope is more likely to be a DY or QY followed by a net negative charge. Anchored synthetic peptides might be expected in general to have a lower and more variable (due to temperature differences etc.) probability of stably adapting the native conformation associated uniquely with the $PrP^{Sc}$ molecule, though that probability might also be expected to increase when the antigenic determinant is closer to the middle of the peptide sequence (for both constraint and contextual reasons). Only three places in the PrP molecule have a negatively charged amino acid, in this case a (Q) or a (D) followed by a tyrosine (Y) and in each case it is followed by a net negative charge. These three places correspond to the three regions to which 15B3 binding was mapped. The initial "DY" or "QY" is present in peptides 61-66, 73-78, and 97-102. Signal can be seen, decreasing when the "DY" is near an end of the peptide, in wells 61-66 (Korth *et al.* Nature, Figure 2). Similarly, signal is present in wells 73-78, though more weakly, but strongest when "QY" is in the middle of the sequence. In fact, it was supposedly only in wells 73-79 in the original Korth *et al.* application (EP0861900), though the figure is of a poor quality and does not unequivocally support this conclusion. Korth *et al.* Nature, Figure 2 also has signal in well 101, again when "QY" is toward the middle of the peptide sequence. From the first (61-66) and the last (73-78) of these sequences a reasonable epitope might appear to be (-)Y(-)(-/+)(-/+), where the net charge after the tyrosine is negative. So, for peptides 61-66, DYEDR (-Y--+), and for 97-102 QYQRE (QYERE in human, used in the immunoprecipitations) (-Y-+-). Peptides 73-78 varies placement of the charge around the

tyrosine slightly: DQYSNQNN (--YX----). The minimal epitope present for binding appears to be at least "-Y" plus another negative charge: peptide 61 (MSRPLIHFGSDYE) and peptide 73 (PNQVYYRPVDQYS), considerably different from the YYR epitope, which presumably relies upon the pi-stacking interaction of the dual tyrosines. However, the unexplained variability between the results in the original European application and the paper in the same assay, combined with the unavailability of the antibody outside the laboratory of origin for testing, call the epitope mapping results into question in general, and, in any event, the Korth *et al.* paper does not suggest, make publicly known or publicly use the YYR epitope. Furthermore, the Korth *et al.* paper itself argues against a simple linear peptide as constituting the epitope for their antibody (p. 76, column 2, lines 12-14).

Again, the 15B3 antibody is, in fact, not available outside Prionics AG, and it is not believed to actually to specifically bind $PrP^{Sc}$ with high affinity, despite the Nature paper data. And, minimally, the 15B3 composition does not meet the claim limitations set by our application. Prionics AG has not in fact solved the problems that the present invention was designed to meet, for example "the availability of antibodies that distinguish $PrP^{C}$ from $PrP^{Sc}$," and no need of digestion. Their Prionics ®-Check WESTERN and Prionics ®-Check LIA both rely on enzymatic digestion of PrP and the use of the 6H4 antibody, not 15B3. This lack of function is further confirmed by persons skilled in the art, for example, Maissen *et al.* Lancet (2001) *357*: 2026 - 2028 (provided in the Supplemental IDS) from the independent Aguzzi lab, a contemporary of the Oesch lab at the University of Zurich during the genesis of Prionics AG and co-author of papers with the Oesch lab (for example, Heppner *et al.* Science. 2001 Oct

5;294(5540):178-82. Epub 2001 Sep 06 and Fischer *et al.* EMBO J. 1996 Mar 15;15(6):1255-64), in the following paragraph (bold added for emphasis) from page 2026:

> Immunochemical procedures, such as western blotting, detect $PrP^{Sc}$, which is a reliable marker of the disease and might be identical with the infectious agent. Such procedures are fast, but not very sensitive. Additionally, since **there are no reagents that discriminate between normal and disease-associated prion protein**, predigestion of samples with proteolytic enzymes is required -- a procedure that increases the complexity of assays, decreases their potential sensitivity, and impairs their amenability to automation.

The 15B3 antibody was actually compared side-by-side with one of our antibodies in the Oesch laboratory at Prionics AG under their conditions. The data indicate notably weak $PrP^{Sc}$ binding by 15B3, just slightly greater than non-specific binding of $PrP^{Sc}$ to control, and superior $PrP^{Sc}$ binding by our own antibodies.

Additionally, the 15B3 antibody is purportedly an IgM (Heppner *et al.*, Science (2001) *294*: 178-182), and although the examiner notes the antibody is "high affinity", there is no claim of such from Korth *et al.*, nor is there evidence of such provided. In fact, IgMs are well known in the art to be of low affinity (see, for example, Janeway CA, Travers P, Walport M, Shlomchik M, Immunobiology $5^{th}$ edition, Garland Publishing, 2001, Figure 10.25). The rejected claims are, in fact, all directed toward high affinity antibodies, a genus of for which there is no reason to believe 15B3 constitutes a species.

Finally, as an epitope, "YYR" is unique and unpredictably short. There is no reason to believe that presentation of the full prion sequence would ever lead to an antibody against this epitope, without its presentation in a restricted context, such as in the peptides of our application. The specification of our application notes YYR as the basis of specific immunoreactivity (p. 4) and the unusual properties of the sequence itself (*pi*-stacking, p. 14-15). As noted in Antibodies in Cell Biology, ed. David J. Asai, Academic Press, San Diego, 1993, p. 20: "In general, peptides below a length of 10 amino acids (Mr ~ 1000) are non-immunogenic when injected in a soluble form." and "Several studies have shown that the size of an antigenic determinant (epitope) of a protein is on the order of four to eight amino acids (Getzoff *et al.*, 1987; Geysen *et al.*, 1987)." Our epitope is three amino acids. The Trilateral Project 24.1 - Biotechnology Comparative Study on Biotechnology Patent Practices examining practices of the USPTO, JPO, and EPO indicated in Section 2 of its report that a partial polypeptide fragment of a larger previously disclosed amino acid sequence utilized as an epitope is novel if the invention related to it has not been previously disclosed in concrete terms and inventive (non-obvious) if it provides a surprising technical property or effect. This is clearly a standard the YYR epitope meets.

These same arguments apply to the Korth *et al.* patent applications.

In sum, given the teachings found in applicants' specification and the plain distinctions between the high affinity anti-YYR antibodies therein and antibodies such as 15B3 and 6H4, it is unreasonable to interpret 15B3 and 6H4 as anticipating the applicants' invention without making significant additional assumptions. Paramithiotis *et al.* provides direct evidence that 6H4 binds

to an epitope distinct from YYR, and 6H4 falls outside the applicants claim limitations. Likewise 15B3 has been tested side-by-side with a YYR antibody and the differing results indicate a different epitope is recognized by 15B3 or 15B3 is of extremely low affinity. In fact, the YYR epitope is not supported by the Korth *et al.* paper as a simple linear epitope for 15B3. 15B3 additionally falls outside of the claim limitations as, at best, a low affinity antibody, if it functions at all. Finally, YYR represents a unique unpredictable short epitope of unusual properties, which could not have been anticipated by Korth *et al.* The claims are clearly distinguishable from the prior art. Accordingly, these rejections should be withdrawn.

## Conclusion

In summary, applicants submit that the claims are now in condition for allowance, and such action is respectfully requested.

If there are any additional charges or any credits, please see the accompanying Petition for Extension of Time for instructions.

Respectfully submitted,

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Attachments